REMARKS

Applicant respectfully requests reconsideration. Claims 42-53, 59-69, 71-73 and 75-80 are pending in this application. No claims have been amended or cancelled. No new matter has been added.

Interview Summary

Applicant and the under-signed attorney thank Examiner Gussow for the telephone interview of December 8, 2008. During the interview, Examiner Gussow indicated that the main objection in the outstanding Office Action pertains to the broad scope of the CpG oligonucleotides being claimed in the application.

Rejection Under 35 U.S.C. 112

Claims 42-53, 59-69, 71-73 and 75-80 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement.

Applicant's fundamental invention is directed to a class of molecules that are useful in the treatment of disease. The instant invention is based on the discovery that the immune system detects bacterial DNA by the presence of unmethylated CpG nucleotides, which can be present in a wide variety of base contexts. Applicant was the first to recognize that synthetic oligonucleotides containing unmethylated CpG irrespective of their sequence or length could replicate these immune activating effects of bacterial DNA. The patent application discloses over 100 different oligonucleotides with unmethylated CpG that can produce an immune response.

The following evidence is presented below in more detail: 1. the pattern of immune response elicited by CpG oligonucleotides and described and exemplified in the specification is predictive of a utility of this class of molecules in the treatment of cancer and 2. CpG oligonucleotides are a class of molecules having diverse sequences, lengths, and backbone composition but a common unmethylated CpG dinucleotide motif that produce such an immune response, as described and exemplified in the specification and confirmed in numerous post-filing publications. The combined evidence is sufficient to support a finding of enablement of the claimed invention. Thus, it is respectfully requested that the rejection be withdrawn.

1. The pattern of immune response elicited by CpG oligonucleotides and described and exemplified in the specification is predictive of a utility of this class of molecules in the treatment of cancer.

The invention relates to the discovery that immunostimulatory CpG oligonucleotides produce a systemic immune response in a subject that is useful in the treatment of cancer. It had been known that certain types of infections and bacterial extracts trigger immune responses that can cause regression of cancers. The present invention is based at least in part on the discovery that the immune stimulatory effects of bacterial DNA result from the presence of unmethylated CpG motifs, which, in contrast, are predominately methylated and thus non-stimulatory in vertebrate DNA. The immune system has thus evolved a defense mechanism against infection that is based on immune recognition of CpG motifs, which trigger a protective immune response. One aspect of the invention is the recognition that the same type of immune response that is triggered through this defense pathway can be directed against cancer, using synthetic oligonucleotides that mimic bacterial DNA. From this discovery of the mechanism of immune activation by bacterial DNA, the invention provides for the use of synthetic oligonucleotides containing these CpG motifs to induce a pattern of immune activation, which is capable of causing tumor regression. Clinical trials involving administration of bacterial DNA to humans demonstrated positive effects in cancer patients. (See e.g., Tokunaga et al Jpn. J. Infect. Dis 52, 1-11, 1999.)

The invention relates to the discovery that a class of molecules having a common structural motif (a CpG dinucleotide) provokes an immune response and when administered to a subject results in an immune response useful in the treatment of cancer. This class of oligonucleotides is described throughout the specification. Data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The experiments demonstrated that the unmethylated CpG dinucleotide was the important component of the oligonucleotides by testing a number of control oligonucleotides in which the C was methylated or the C and/or G were replaced with other dinucleotides. The data in the application, including that represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. In view of the data in the specification the skilled artisan would have expected that virtually every CpG containing oligonucleotide would have the ability to

provoke an immune response. Although some oligonucleotides may work better than others, it is expected that in general CpG oligonucleotides are immunostimulatory under the appropriate conditions.

At the time the priority patent application was filed it was known in the art that induction of interferon-γ (IFN-γ), IL-12, and IL-6, as well as NK cell activation was useful in the treatment of cancer. Applicant previously presented arguments that rebutted the rejections of record including the citation of references to demonstrate a correlation between the data in the specification and the skilled artisan's understanding at the time of the invention that such data supported the usefulness of the CpG oligonucleotides in the treatment of cancer. Applicant reiterates those arguments here and requests that they be addressed or the rejection withdrawn. The following summaries of references published prior to or around the priority date of the instant application describe the state of the art with respect to immune system activation and the treatment of cancer.

Trinchieri et al., Blood, V.84, December 15, 1994, p. 4008 is a review article describing IL-12 in the production of cytotoxic lymphocytes. Page 4021 describes the role of IL-12 in anti-tumor immunity. Specifically, it is taught that "studies using transplantable tumors in experimental animals have shown a dramatic affect of IL-12 in decreasing tumor growth and metastasis formation and in significantly delaying death. Systemic Daily Treatment (5 days per week) had a significant inhibitory affect on the growth of metastasis induced by intravenous injection of B16 melanoma cells and efficiently inhibited the growth of subcutaneously injected tumors, even when treatment was initiated two weeks after tumor inoculation. An inhibitory affect of IL-12 on tumor growth, with a greater than two-fold increase in survival of inoculated animals, was also observed with the reticulum cell sarcoma M5076 and with the renal cell adenocarcinoma renca. In this latter tumor, complete remission, especially with peritumoral injection of IL-12, was observed in some animals; reinjection of the renca cells in the "cured" animals resulted in delayed growth of the tumor, suggesting that IL-12 may induce a memory immune response against the tumor" (paragraph spanning 4021-4022, references omitted).

Brunda et al. Journal Leukocyte Biology, V.55, February 1994 is a review article describing IL-12. Pages 285-286 of Brunda et al. describe the use of IL-12 in vivo in numerous murine tumor models. It is taught that "a large body of experimental evidence has now been accumulated

demonstrating that IL-12 has potent antimetastatic and antitumor activity in a number of murine tumor models. The therapeutic activity of IL-12 has been observed in four of four murine metastasis models, including both pulmonary and hepatic metastases." (page 285, first column, last paragraph).

U.S. Patent No. 4,883,662 issued on November 28, 1989, describes an in vivo method for increasing NK cells in the blood of cancer patients because such NK cells have known activity against tumor cells (abstract). In the summary of the invention it is taught that "it has been established that increasing such natural killer cells is an important component of the immune system, and that accordingly the present method should be a decided advantage in cancer treatment."

Hayashi et al., Proceeding of the Japan Academy, Series B: Physical and Biological Sciences, 1994, 70, 205, describes immunotherapy for the treatment of cancer. The abstract teaches that immunotherapy with BCG-CWS results in IFN-γ induction. It is further taught that cancer patients experiencing IFN-γ induction and/or strong skin reaction survived for longer periods of time than those patients showing no IFN-γ induction, who died after a short period.

The above described references were published prior to or around the priority date of the instant application. These references establish that one of skill in the art would have recognized the utility of a CpG containing oligonucleotide which is effective in inducing IL-12, IFN-γ and NK cell activation in a method of treating or preventing cancer in a subject. Thus, at the time of the invention the data presented in the specification would have been sufficient to demonstrate to one of skill in the art that unmethylated CpG oligonucleotides are useful in the treatment of cancer.

2. CpG oligonucleotides are a class of molecules having diverse sequences, lengths, and backbone composition but a common unmethylated CpG dinucleotide motif that produce such an immune response, as described and exemplified in the specification and confirmed in numerous post-filing publications

In the specification, Applicants have taught that oligonucleotides containing an unmethylated CpG dinucleotide produced an immune response that is consistent with the treatment

of cancer. Applicants have demonstrated that oligonucleotides containing an unmethylated CpG are effective at stimulating B-cell proliferation (Table 1, and Examples 1-3), IgM secretion (Example 2), induction of IL-6, IL-12, and IFN-γ (page 17, 1st paragraph, pages 30-31, and Example 8) and induction of NK cell activity (page 17, 2nd paragraph, pages 36-41, and Example 4). Applicants have provided numerous examples of oligonucleotides falling within the genus of molecules. See for example page 15-17, and Table1. Over 100 ODN are described in various tables and figures in the specification. Significant amounts of data demonstrating the specific effects of CpG oligonucleotides are provided in the specification. For Example with respect to the formula $X_1X_2CGX_3X_4$, the specification includes examples with data showing changes in B cell activation or cytokine induction of ODN wherein X_1 is G, C, A, or T, X_2 is T, A, G, or C, X_3 is T, C, G, or A or X_4 is T, C, or G (Tables 1, 3 and 5). The data confirms the specificity of the claimed CpG motif by showing oligonucleotides having an unmethylated CpG dinucleotide are capable of inducing an immune response consistent with the treatment of cancer.

The ability of CpG oligonucleotides to induce an immune response has also been demonstrated in other applications filed by Applicant. For example, US Patent Application 2005/0059619 describes a class of soft or semi-soft CpG immunostimulatory oligonucleotides that are useful for stimulating an immune response. Semi-soft oligonucleotides have modified backbones that include mixtures of phosphorothioate and phosphodiester or phosphodiester-like internucleotide linkages. Oligonucleotides comprising varied sequences and lengths were able to induce cytokine secretion and activate NK cells (See examples 1-4, 10). Semi-soft oligonucleotides of reduced length (16,17, and 18-mers) were also observed to be immunostimulatory in vitro (Example 12). Moreover, the efficacy of some oligonucleotides were tested *in vivo* in three different cancer models (murine renca, Lewis lung carcinoma and neuroblastoma) and found to enhance the survival of mice bearing these cancers.

In addition, US Patent Application 2006/0211644 demonstrates the ability of different short CpG oligonucleotides and oligonucleotides with different internucleotide linkages to induce the immunostimulatory response characterized by cytokine induction and activation of immune cells as observed in the present invention (See Examples). For example short ODN having semi-soft or fully phosphorothioate internucleotide linkages demonstrate TLR9 activity and cytokine induction

at different concentrations as shown in Examples 1-3 (ODN ranging in size from 2 nucleotides to 24 nucleotides in length were tested). The ability of a 2 nucleotide ODN with a C linked to a G by a phosphodiester internucleotide linkage (ODN SEQ ID NO.: 31) to induce IFN-alpha levels over background was even observed. ODNs of 5, 6, and 7 nucleotides in length were also observed to induce IFN-alpha in an in vitro assay.

US Patent Application 2006/0140875 includes data demonstrating the ability of specific C-class semi-soft CpG oligonucleotides to induce an immunostimulatory response characterized by cytokine induction and activation of immune cells as observed in the present invention (See Examples). SEQ ID Nos 1-6 and -23, having different lengths and sequences were examined for the ability to induce TLR9 activation and induce cytokine expression in vitro. Additionally SEQ ID No. 1-3 and 7 were demonstrated to have in vivo activity, for example in cytokine induction and asthma models.

US Patent Application 2008/0045473 describes P-class ODN. 30 ODN were designed and tested, including B-class, C-Class and P-Class ODN to demonstrate immunostimulatory activity.

US Patent Application Serial No. 60/964477 and corresponding US utility 12/190,402 include in vivo data using CpG ODN in cancer models. The Examples demonstrated that the tested ODN (SEQ ID NOs. 2-4) were activators of pDC, PBMC, B cells and NK cells in vitro as well as cytokine induction. The same ODN were observed to induce cellular activation in draining lymph node in vivo. Example 7 depicts treatment of tumors in vivo by CpG ODN using Lewis Lung Carcinoma and Neuroblastoma models. Post tumor induction by both SEQ ID NOs 2 and 3 induced a high percent survival.

Regardless of the sequence composition and the length, different CpG oligonucleotides were found to be immunostimulatory as compared to control. The fact that some CpG oligonucleotides may not be as potent in their immunostimulation as compared to others does not negate the enablement of CpG oligonucleotides as a class of molecules that can induce an immune response. Applicant has clearly demonstrated that CpG oligonucleotides irrespective of their sequence and length can produce an immune response characterized by cytokine induction and activation of immune cells which collectively is useful in the treatment of diseases such as cancer.

The Examiner asserts that "the specification does not teach those skilled in the art how to make and use the full scope of the claimed invention, which is the treatment of cancer comprising administering CpG immunostimulatory oligonucleotides comprising 8 to 100 nucleotides in length, without undue experimentation." To this end, the Examiner has cited several references which allegedly demonstrate the inability of CpG-containing oligonucleotides to treat cancer. Applicant has addressed these references and has clearly established that their teachings overall support the use of CpG oligonucleotides in the treatment of cancer. Miscellaneous statements in references referring to future work, fine-tuning, optimization or additional experimentation to prove clinical efficacy do not support a finding of unpredictability of the claimed invention. For example, Weiner (Leukocyte Biology, 2000, 68: 455-465) has been cited as indicating that we don't understand the molecular mechanisms responsible for the effects of CpG oligonucleotides and that further work is needed. Knowledge of the mechanism of action is irrelevant, particularly in view of the detailed knowledge at the time the patent application was filed of the cellular effects of CpG oligonucleotides. Moreover, Weiner on the whole supports the effectiveness of CpG oligonucleotides when used alone or in combination with other agents.

Krieg (Nature, 1995, 374: 546-549) was also cited for teaching that CpG oligonucleotides can be used in immunotherapy of tumors, though many or most may be NK resistant. Applicant cannot identify such a teaching in Krieg et al. Page 117, column 2 is cited in support of this teaching. However the reference is found on pages 546-549. Clarification of the support for this assertion is requested.

On page 7 of the Office Action the Examiner maintains that Agrawal et al (Trends in Mol Med. 2002, 8: 114-121) teaches that different effects are observed with different CpG ODN and that Ballas et al (J. of Immunology, 2001, 167:4878-4886) teaches a single ODN can't be used for all cancers. CpG oligonucleotides may produce variant results, with some oligonucleotides producing more potent immune stimulation and others preferentially activating certain subsets of immune cells. However, the fact that the invention may require further optimization does not negate enablement. "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re: Angstadt 537 F.2D 498, 504, 190 USPQ 124, 129, (CCPA 1976)" "The fact the experimentation may be complex does not necessarily make it

undue. If the art typically engages in such experimentation. In re: Certain limited-charge cell culture microcarriers, 221 USPQ 1165, 1174) Int'l Trade Comm'n 1983)." (MPEP Section 2164.01). Given the fact that even commercially available FDA-approved drugs are subject to further research and development, routine experiments undertaken to understand the medicinal chemistry potential cannot be considered as "undue experimentation".

The instant invention is directed to a class of molecules comprising unmethylated CpG oligonucleotides of various sequence composition and length that have been shown to induce a characteristic immune response An important factor to consider is that currently at least 4 different CpG oligonucleotides have been or are being tested in clinical trials in the therapy of cancer. In Table 2 on page 478 of Krieg (Nat. Revs. 2006 v. 5), the human clinical trials being conducted or completed as of 2006 are listed. If the treatment of cancer using CpG oligonucleotides were so unpredictable, in the years following the invention, that the claims were not enabled, it seems highly unlikely that the FDA and regulatory agencies in other countries would allow testing of these compounds in humans for cancer therapy. The fact that an author suggests that the medicinal chemistry of this class of molecules needs further fine-tuning at a later date does not indicate that the claimed invention lacks enablement.

Accordingly, withdrawal of the rejection of claims 42-53, 59-69, 71-73, and 75-78 under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70021US01.

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Respectfully submitted,

By _____

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